REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons which follow.

Applicant acknowledges the withdrawal of the rejection of claims 23-27, 29, 30, 33, 40 and 41 under 35 U.S.C. §112, second paragraph, and rejoining of claims 30 and 33 for the examination on the merits. Claims 23-26, 29 and 30 are confirmed to be free of prior at.

However, the examiner has maintained the position that claims 34, 35 and 44 are not drawn to the elected species and thus will not be rejoined. Furthermore, the examiner has refused to accord the earlier filing date to claims 1-6, 11, 16-18, 20, 31-34, 36, 39, 42-44, 46 and 49-52. Thus, the examiner has maintained the previous rejections of claims 1-7, 14, 36-41, 45, 46 and 49-52 as obvious over various cited references including Iwasa et al. Finally, claims 1-6, 11, 12, 16-18, 20, 31-34, 36, 39, 42-44, 46 and 49-53 are rejected for obviousness-type double patenting. While not acquiescing to the propriety of the examiner's position in these rejections or objections, applicant has obviated all of these rejections by canceling claims 1-22, 27, 28 and 31-53. Cancellation of these claims is made solely to expedite the prosecution of this case and subject matter of these cancelled claims will be prosecuted in a continuation application. Claims 23-26 have been rewritten as independent claims by incorporating the recitation of claim 1. Because the remaining claims 23-26, 29 and 30 are free of prior art and are not subjected to any rejections or objections for formality reasons, applicant believes that the present application is in condition for allowance. Thus, an early notice to this effect is earnestly solicited.

The examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

23. (Amended) A [The] method [of claim 1, wherein the targeting protein comprises] for targeting a therapeutic agent to a target site in a patient, comprising the steps of:

(a) administering to the patient an effective amount for targeting of at least one multispecific targeting protein comprising at least two first binding sites which specifically bind to the same or different epitopes of the same or different substance produced by or associated with the target site and present at the target site, and at least one second binding site which specifically binds to an epitope of at least one enzyme, wherein binding between the targeting protein and the enzyme does not interfere with enzyme activity;

(b) optionally, administering to the patient an amount effective for clearance of a first clearing composition comprising a clearing agent which clears non-localized targeting protein from circulation;

(c) administering to the patient an effective amount for enzyme activity of the enzyme, such that the targeting protein binds the enzyme to form a non-covalent targeting protein-enzyme conjugate in situ;

(d) optionally, administering to the patient an amount effective for clearance of a second clearing composition comprising a clearing agent which clears non-localized targeting protein, non-localized enzyme, or non-localized targeting protein-enzyme conjugate from circulation;

(e) administering to the patient at least one serum-soluble prodrug composition, wherein the enzyme administered in step (c) acts on the prodrug to release a therapeutic agent that is less soluble in serum than the prodrug, and wherein the therapeutic agent partitions out the target site that it accretes at the target site to a greater extent than would the prodrug, thereby providing therapeutic agent at the target site.

24. (Amended) A [The] method [of claim 1, wherein step (a) comprises administering] for targeting a therapeutic agent to a target site in a patient, comprising the steps of:

(a) administering to the patient an effective amount for targeting of at least two different multispecific targeting proteins each of which [comprise] comprises a first binding site which specifically binds to an epitope of a different substance produced by or associated with the target site and present at the target site, and each of which comprises at least one second binding site which specifically binds to an epitope of at least one enzyme, wherein binding between the targeting protein and the enzyme does not interfere with enzyme activity;

(b) optionally, administering to the patient an amount effective for clearance of a first clearing composition comprising a clearing agent which clears non-localized targeting protein from circulation;

(c) administering to the patient an effective amount for enzyme activity of the enzyme, such that the targeting protein binds the enzyme to form a non-covalent targeting protein-enzyme conjugate in situ;

(d) optionally, administering to the patient an amount effective for clearance of a second clearing composition comprising a clearing agent which clears non-localized targeting protein, non-localized enzyme, or non-localized targeting protein-enzyme conjugate from circulation;

(e) administering to the patient at least one serum-soluble prodrug composition, wherein the enzyme administered in step (c) acts on the prodrug to release a therapeutic agent that is less soluble in serum than the prodrug, and wherein the therapeutic agent partitions out the target site that it accretes at the target site to a greater extent than would the prodrug, thereby providing therapeutic agent at the target site.

25. (Amended) A [The] method [of claim 1, wherein the targeting protein comprises] for targeting a therapeutic agent to a target site in a patient, comprising the steps of:

(a) administering to the patient an effective amount for targeting of at least one multispecific targeting protein comprising at least one first binding site which specifically binds to at least one epitope of at least one substance produced by or associated with the target site and present at the target site, and at least two second binding sites which specifically bind to different enzymes, [and wherein step (c)

comprises administering the different enzymes] wherein binding between the targeting protein and the enzyme does not interfere with enzyme activity;

(b) optionally, administering to the patient an amount effective for clearance of a first clearing composition comprising a clearing agent which clears non-localized targeting protein from circulation;

(c) administering to the patient an effective amount for enzyme activity of the different enzymes, such that the targeting protein binds the enzymes to form a non-covalent targeting protein-enzyme conjugate in situ;

(d) optionally, administering to the patient an amount effective for clearance of a second clearing composition comprising a clearing agent which clears non-localized targeting protein, non-localized enzyme, or non-localized targeting protein-enzyme conjugate from circulation;

(e) administering to the patient at least one serum-soluble prodrug composition, wherein the enzyme administered in step (c) acts on the prodrug to release a therapeutic agent that is less soluble in serum than the prodrug, and wherein the therapeutic agent partitions out the target site that it accretes at the target site to a greater extent than would the prodrug, thereby providing therapeutic agent at the target site.

26. (Amended) A [The] method [of claim 1, wherein step (a) comprises administering] for targeting a therapeutic agent to a target site in a patient, comprising the steps of:

(a) administering to the patient an effective amount for targeting of at least two different multispecific targeting proteins each of which comprises at least one first binding site which specifically binds to at least one epitope of at least one substance produced by or associated with the target site and present at the target site, and each of which [comprise] comprises a second binding site which specifically binds to an epitope of a different enzyme, wherein binding between the targeting protein and the enzyme does not interfere with enzyme activity;

(b) optionally, administering to the patient an amount effective for clearance of a first clearing composition comprising a clearing agent which clears non-localized targeting protein from circulation;

(c) administering to the patient an effective amount for enzyme activity of the different enzymes, such that the targeting protein binds the enzymes to form a non-covalent targeting protein-enzyme conjugate in situ;

(d) optionally, administering to the patient an amount effective for clearance of a second clearing composition comprising a clearing agent which clears non-localized targeting protein, non-localized enzyme, or non-localized targeting protein-enzyme conjugate from circulation;

(e) administering to the patient at least one serum-soluble prodrug composition, wherein the enzyme administered in step (c) acts on the prodrug to release a therapeutic agent that is less soluble in serum than the prodrug, and wherein the therapeutic agent partitions out the target site that it accretes at the target site to a greater extent than would the prodrug, thereby providing therapeutic agent at the target site.